REMARKS

Status of the Claims:

Claims 1-28 and 30-78 are pending in the present application. Claim 29 has been canceled without prejudice to or disclaimer of the subject matter contained therein. Claims 1, 10, 16, 20, 32, 34, and 37 have been amended to recite that the interferon-β (IFN-β) is biologically active. Support for this amendment may be found throughout the specification, for example, on line 12 of page 8 and lines 11-12 of page 11. Independent claim 13 has been amended to depend from claim 10, as the distinction between these compositions resides in the specific limitation that the composition of claim 13 further comprises sodium chloride to render it isotonic. Claim 6 has been amended to correct antecedent basis in view of the amendments to claim 1, and claim 24 has been amended to recite the sequence identifier numbers for mature native human IFN-β (SEQ ID NO:1) and the C17S mutein of mature native human IFN-β (SEQ ID NO:2) described on lines 21-23 of page 7 and lines 1-3 of page 8, respectively, of the specification.

New claims 41-78 have been added. Support for new claims 41, 51, 57, 60, 69, 73, and 76 is found on lines 12-15 of page 9 and lines 1-4 of page 10 of the specification. Support for new claims 42, 52, 55, 58, 61, 63, 70, 74, and 77 is found on lines 23-26 of page 5 of the specification. Support for new claims 43, 53, 56, 59, 62, 64, 71, 75, and 78 is found in Figure 17. Support for new claims 44-50 and 65-68 is found in Figures 13, 14(B), and lines 5-7 of page 7 of the specification. Support for new claims 54 and 72 is found on lines 21-23 of page 7 and on lines 1-3 of page 8 of the specification. Accordingly, the foregoing amendments do not add new matter; their entry is therefore respectfully requested.

The specification has been amended to provide sequence identifiers for the amino acid sequences of mature native human IFN-β (SEQ ID NO:1) and a C17S mutein of mature native human IFN-β (SEQ ID NO:2) described on lines 21-23 of page 7 and lines 1-3 of page 8, respectively, of the specification. A new Sequence Listing setting forth the recited sequences is filed concurrently herewith. These sequences are described in U.S. Patent No. 5,814,485, which is incorporated by reference in the present application. *See*, lines 22-23 on page 7 of the

specification. Accordingly, no new matter is added by way of this amendment or presentation of this Sequence Listing. Entry of this Sequence Listing and these amendments to the specification is respectfully requested.

Reexamination and reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

The Rejections Under 35 U.S.C. § 102 Should Be Withdrawn

Claims 1-4, 6-9, 26, 29-33, and 37 have been rejected under 35 U.S.C. § 102(b) on the grounds that they are anticipated by WO 95/31479 (Platz *et al.*). Claims 1, 2, 4, 5, 7-9, 26, 29-33, and 37 are also rejected under 35 U.S.C. § 102(b) on the grounds that they are anticipated by WO 95/31213 (Samaritani *et al.*). The rejections are respectfully traversed for the reasons described below.

WO 95/31479 discloses pharmaceutical formulations containing IFN-β and mannitol. This patent publication also teaches that such formulations may be spray-dried to produce a powdered composition. However, the publication does not teach the use of highly purified mannitol in these pharmaceutical formulations.

WO 95/31213 discloses pharmaceutical formulations containing IFN-β, including recombinant IFN-β and a polyol such as mannitol and methods for their preparation. In some embodiments, the formulation contains human albumin. However, this publication does not teach the use of highly purified mannitol in the disclosed formulations.

Claims 1-9, 26, 29-33, and 37 of the present application include the limitation that the claimed composition comprises highly purified mannitol. Highly purified mannitol is described on lines 23-25 of page 5 of the specification as mannitol having a reducing activity that is less than 20 parts per million. Figure 17 of the present application demonstrates that USP-grade mannitol that has not been highly purified has a reducing activity well above 20 parts per million.

The use of highly purified mannitol in the compositions of the present invention results in improved stability during storage in comparison with IFN-β compositions that contain mannitol that is not highly purified. Compare, for example, the IFN-β adducts seen in USP mannitol-

formulated IFN-β in Figure 11 with those observed for an IFN-β formulation comprising highly purified mannitol in Figure 9. The highly purified mannitol IFN-β compositions of the present invention are characterized by the absence of additional peaks that are observed in USP mannitol-formulated IFN-β. *See also,* line 25 of page 6 through line 7 of page 7 and lines 15-21 of page 22 of the specification.

A claim is anticipated only if each and every element set forth in the claim is found in a single prior art reference. In the present case, neither WO 95/31479 nor WO 95/31213 teach the use of highly purified mannitol in IFN-β formulations. Accordingly, these publications do not anticipate the invention of claims 1-9, 26, 29-33, and 37.

In view of the above arguments, all grounds for rejection under 35 U.S.C. § 102 have been overcome. Reconsideration and withdrawal of these rejections are therefore respectfully requested.

The Rejections Under 35 U.S.C. § 103 Should Be Withdrawn

Claims 10-25 have been rejected under 35 U.S.C. § 103(a) on the grounds that they are obvious over WO 95/31479 (Platz *et al.*) in view of U.S. Patent No. 4,808,705 to Ferris. The rejection is respectfully traversed for the reasons described below.

As noted above, Platz *et al.* teach pharmaceutical formulations containing IFN-β and mannitol. Platz *et al.* also teach that such formulations may be spray-dried. Ferris teaches the use of mannitol in a pharmaceutical composition containing ricin toxin A chain immunoconjugates. Neither Platz *et al.* nor Ferris teach the use of highly purified mannitol in a pharmaceutical formulation.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested in the prior art. *Manual of Patent Examining Procedure* § 2143.03, citing *In re Royka*, 180 USPQ 580 (CCPA 1974). Furthermore, all words in a claim must be considered in judging the patentability of that claim against the art. *Id.* citing *In re Wilson*, 165 USPQ 494, 496 (CCPA 1970). In the present case, neither of the cited references teaches or suggests the claim limitation of highly purified mannitol. Accordingly, there is no *prima facie* case of obviousness established for claims 10-25.

Claims 27 and 28 have been rejected under 35 U.S.C. § 103(a) as being obvious over WO 95/31213. This rejection is respectfully traversed.

The Examiner argues that WO 95/31213 teaches storage of the disclosed formulations in a hermetically sealed container under sterile conditions prior to use and that the syringe recited in claims 27 and 28 would fall within this description. However, claims 27 and 28 depend from claim 1, and claim 1 recites the use of highly purified mannitol. WO 95/31213 does not teach or suggest the use of highly purified mannitol. Accordingly, the cited reference does not teach every limitation of claims 27 and 28, and no *prima facie* case of obviousness has been established for these claims.

Claims 34, 35, and 38-40 are rejected under 35 U.S.C. § 103(a) on the grounds that they are unpatentable over WO 95/31213 in further view of U.S. Patent No. 4,462,940 to Hanisch *et al.* The rejection is respectfully traversed for the reasons described below.

U.S. Patent No. 4,462,940 teaches the purification of interferon-β by the removal of salt and detergent on Sephacryl and TSK resins and the subsequent addition of albumin at pH 11. The Examiner argues that it would be obvious to one of skill in the art to modify the purification method taught in the '940 patent to include the step of adding mannitol in view of the teachings of WO 95/31213 regarding the use of mannitol in an interferon-β formulation. However, claims 34, 35, and 38-40 recite the step of adding a solution of highly purified mannitol, and neither WO 95/31213 nor U.S. Patent No. 4,462,940 teach or suggest the addition of highly purified mannitol to IFN-β formulations. In the absence of any teaching or suggestion regarding this claim limitation, the combination of references does not establish a *prima facie* case of obviousness for these claims.

In view of the above arguments, all grounds for rejection under 35 U.S.C. § 103 have been overcome. Reconsideration and withdrawal of these rejections are therefore respectfully requested.

The Rejection Under 35 U.S.C. § 112, Second Paragraph, Should Be Withdrawn

Claims 1-9, 26-29, and 32-40 have been rejected under 35 U.S.C. § 112, second paragraph on the grounds that they are indefinite for reciting the term "variants." Applicants respectfully submit that the term "variants" is not indefinite. This term is defined in the specification on lines 10-13 of page 7, which states that "[h]uman IFN-β variants, which may be naturally occurring (e.g., allelic variants that occur at the IFN-β locus) or recombinantly produced, have amino acid sequences that are the same as, similar to, or substantially similar to the mature native IFN-β sequence." The specification provides examples of at least thirteen IFN-β variants on line 21 of page 7 through line 9 of page 8, including the Cys17Ser mutein recited in the claims. Guidance for making IFN-β variants is provided on line 10 of page 8 through line 11 of page 9. Therefore, one of skill in the art, when reading original claims 1-9, 26-29, and 32-40 in light of the supporting specification, would be able to ascertain the scope of these claims.

However, solely for the purpose of clarification, and not for any reason related to patentability, claims 1, 32, 34, and 37 have been amended to recite "biologically active IFN-β." The term "IFN-β" as used in the present application encompasses IFN-β and variants thereof as indicated on lines 9-10 of page 7 of the specification. The specification defines biologically active IFN-β variants on lines 11-23 of page 11. Support for this amendment may be found throughout the specification, for example, on line 12 of page 8 and lines 11-12 of page 11. Accordingly, the scope of the amended claims would also be clear to those of skill in the art.

In view of the above arguments and amendments, all grounds for rejection under 35 U.S.C. § 112, second paragraph, have been obviated or overcome. Reconsideration and withdrawal of the rejection are therefore respectfully requested.

New Claims Presented

New claims 41-78 have been presented. These claims are drawn to specific embodiments encompassed by the broader claims from which they depend. Support for these claims resides in the specification as noted above. All of these claims recite the use of highly purified mannitol.

Accordingly, for the reasons noted above, the cited prior art does not teach or suggest the subject matter recited in these new claims.

CONCLUSION

It is believed that all the rejections have been obviated or overcome and the claims are in condition for allowance. Early notice to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject Application, the Examiner is invited to call the undersigned agent.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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